AMENDMENTS TO THE SPECIFICATION

Please replace this title on page 1 of the specification with the following amended title:
-- MODIFIED ~~BYRODIN~~ BRYODIN 1 WITH REDUCED IMMUNOGENICITY --

On page 1, before the heading "FIELD OF THE INVENTION" please add the following paragraph:
-- This application is the National Stage of International Application No. PCT/EP03/06055, filed on June 10, 3002. --

Please replace the paragraph beginning at line 5 on page 5 of the specification with the following amended paragraph:
-- One of these therapeutically valuable molecules is bryodin 1. The present invention provides for modified forms of bryodin 1 with one or more T cell epitopes removed. The sequence of bryodin 1 protein (SEQ ID NO: 1) as given by Gawlak ~~et al~~ *et al.* [Gawlak, S. ~~et al (1997) *Biochemistry* 36:3095-3103~~ *et al.* (1997) *Biochemistry* 36:3095-3103] is depicted in single-letter code as follows:
DVSFRLSGATTTSYGVFIKNLREALPYERKVYNIPLLRSSISGSGRYTLLHLTNYADETIS
VAVDVTNVYIMGYLAGDVSYFFNEASATEAAKFVFKDAKKKVTLPYSGNYERLQTAA
GKIRENIPLGLPALDSAITTLYYYTASSAASALLVLIQSTAESARYKFIEQQIGKRVDKTFL
PSLATISLENNWSALSKQIQIASTNNGQFESPVVLIDGNNQRVSITNASARVVTSNIALLL
NRNNIAAIGEDISMTLIGFEHGLYGI (SEQ ID NO: 1). --

Please replace the paragraph beginning at line 26 on page 5 of the specification with the following amended paragraph:
-- Others have provided bryodin molecules and in particular recombinant bryodin 1 [US,5,541,110; US,5,932,447], but these teachings do not recognise the importance of T cell epitopes to the immunogenic properties of the protein nor have been conceived to directly influence said properties in a specific and controlled way according to the scheme of the present invention. By contrast, the PCT patent application WO00/34317 published 15-June 2000

discloses a modified bryodin 1 molecule including substitutions at positions 5,6, 18, 27, 111, 164, 216, 222, 237 and 249 of SEQ ID NO: 1. The substitutions have been selected on the basis of an *in silico* motif matching tool and do not address the most biologically relevant MHC class II epitopes detected in a biological assay and which are for the first time disclosed herein. Moreover where the present invention discloses sequences to be considered as the biologically relevant epitopes in the subject molecule the inventors have recognized largely identical sequences in related proteins namely α-trichosanthin, α-momorcharin and ß-momorcharin which accordingly by structural homology are relevant epitopes also in these proteins. --

Please replace the paragraph beginning at line 9 on page 8 of the specification with the following amended paragraph:

-- an accordingly specified molecule wherein alteration is conducted at one or more residues from any or all of the string of contiguous residues of sequences (a), (b), (c), (d), or (e) as below wherein said sequences are derived from the bryodin 1 wild-type sequence where using single letter code;

(a) = RYTLLHLTNYADETISVAVDV (R1) (SEQ ID NO: 2),

(b) = ATEAAKFVFKDAKKK (R2) (SEQ ID NO: 3),

(c) = ERLQTAAGKIRENIPLGLPALDSA (R3) (SEQ ID NO: 4),

(d) = ITTLYYYTASSAASALLVLIQSTAESA (R4) (SEQ ID NO: 5),

(e) = ATISLENNWSALSKQIQIAST (R5) (SEQ ID NO: 6), --

Please replace the paragraph beginning at line 1 on page 11 of the specification with the following amended paragraph:

-- a bryodin 1 molecule of structure according to Formula I (SEQ ID NO: 7):

X^0DVSFRLSGATTTSYGVFIKNLREALPYERKVYNIPLLRSSISGSGRYX^1X^2LX^3LTX^4X^5A DETX^6SVAX^7DX^8TNVYIMGYLAGDVSYFFNEASATEAAKX^9X^{10}FKDAKKKX^{11}TLPYSG NYERX^{12}QTX^{13}A$X^{14}X^{15}X^{16}X^{17}$ENX^{18}PLGX^{19}PAX^{20}DSAX^{21}TTX^{22}Y$X^{23}X^{24}$TASSAASA$X^{25}X^{26}X^{27}X^{28}$IQSTAESARYKFIEQQIGKRVDKTFLPSLATX^{29}SX^{30}ENNWSAX^{31}SX^{32}QX^{33}QX^{34}AS TNNGQFESPVVLIDGNNQRVSITNASARVVTSNIALLLNRNNIAAIGEDISMTLIGFEHGL YGI

wherein

X^0 is hydrogen or a targeting moiety such as an antibody domain;

X^1 is most preferably A but G and P are also considered;

X^2 is most preferably M but A, G, P and I are also considered;

X^3 is most preferably A but G and P are also considered;

X^4 is most preferably P but Y is also considered;

X^5 is most preferably T but S is also considered;

X^6 is P;

X^7 is most preferably A but P and G are also considered;

X^8 is most preferably A but P and G are also considered;

X^9 is most preferably A but P, G, H, D, E, N, Q, K, R, S and T are also considered;

X^{10} is most preferably A but P and G are also considered;

X^{11} is most preferably A but P and G are also considered;

X^{12} is most preferably A but P, S, T, H and K are also considered;

X^{13} is T;

X^{14} is H;

X^{15} is S;

X^{16} is most preferably A, but S, T, P, N, D, E, G, H, K and Q are also considered;

X^{17} is T;

X^{18} is most preferably A but P is also considered;

X^{19} is most preferably A but I, F, G, M, P, V, W and Y are also considered;

X^{20} is most preferably F but P and W are also considered;

X^{21} is most preferably A but P and G are also considered;

X^{22} is most preferably G but A and P are also considered;

X^{23} is most preferably G but A and P are also considered;

X^{24} is most preferably A but P and G are also considered;

X^{25} is most preferably A but P, G, S and T are also considered;

X^{26} is most preferably A but I, M, S, T, P and G are also considered;

X^{27} is most preferably A but G and P are also considered;

X^{28} is most preferably S but A, G, P, T, H, D, N, Q, K and R are also considered;

X^{29} is most preferably T but A, G, S, P, H, K, R, D, E, N and Q are also considered;
X^{30} is most preferably A but G, S, T, P, K, R, H, D, E, N and Q are also considered;
X^{31} is Q;
X^{32} is most preferably H but D, E, F, L, N, P, S, W and Y are also considered;
X^{33} is most preferably T but A, G, P, D, E, H, K, R, N, Q, S and T are also considered;
X^{34} is most preferably D,
and whereby simultaneously
$X^1 = T$, $X^2 = L$, $X^3 = H$, $X^4 = N$, $X^5 = Y$, $X^6 = I$, $X^7 = V$, $X^8 = V$, $X^9 = F$, $X^{10} = V$, $X^{11} = V$,
$X^{12} = L$, $X^{13} = A$, $X^{14} = G$, $X^{15} = K$, $X^{16} = I$, $X^{17} = R$, $X^{18} = I$, $X^{19} = L$, $X^{20} = L$, $X^{21} = I$, $X^{22} = L$, $X^{23} = Y$,
$X^{24} = Y$, $X^{25} = L$, $X^{26} = L$, $X^{27} = V$, $X^{28} = L$, $X^{29} = I$, $X^{30} = L$, $X^{31} = L$, $X^{32} = K$,
$X^{33} = I$ and $X^{34} = I$
are excluded. --

Please replace the paragraph beginning at line 29 on page 15 of the specification with the following amended paragraph:

-- It is most preferred to provide a bryodin 1 molecule in which amino acid modification (e.g. a substitution) is conducted within the most immunogenic regions of the parent molecule. The inventors herein have discovered that the most immunogenic regions of the bryodin 1 molecule in man are confined to at least five regions R1 – R5 encompassing residues 46-66; 88-102; 112-135; 136-162 and178-204 of SEQ ID NO: 1 comprising respectively amino acid sequences;
R1) RYTLLHLTNYADETISVAVDV (SEQ ID NO: 2);
R2) ATEAAKFVFKDAKKK (SEQ ID NO: 3);
R3) ERLQTAAGKIRENIPLGLPALDSA (SEQ ID NO: 4);
R4) ITTLYYYTASSAASALLVLIQSTAESA (SEQ ID NO: 5) and
R5) ATISLENNWSALSKQIQIAST (SEQ ID NO: 6). --

Please replace the paragraph beginning at line 13 on page 24 of the specification with the following amended paragraph:

-- **FIGURE 3** indicates the sequence elements R1 (SEQ ID NO: 2), R2 (SEQ ID NO: 3), R3 (SEQ ID NO: 4), R4 (SEQ ID NO: 5) and R5 (SEQ ID NO: 6) from the bryodin 1 (1BRY)

sequence (SEQ ID NO: 1) which give a stimulation index of 2.0 or greater in PBMC preparations from 2 or more donors PBMC using the naïve human *in vitro* T-cell assay of EXAMPLE 2. Corresponding ~~sequences from~~ mutations in related proteins α-trichosanthin (1TCS), α-momorcharin (1MOM) and ß-momorcharin (1CF5) are shown beneath each bryodin 1 sequence. Sequences of the related proteins are identical to bryodin 1 except where indicated. Amino acids are depicted using single letter code. --

Please replace the paragraph beginning at line 6 on page 25 of the specification with the following amended paragraph:

-- **FIGURE 6** is a depiction of the MHC class II ligands identified within epitope region R1 (SEQ ID NO: 2, shown vertically in the first column). Ligands are identified using the *in silico* system of EXAMPLE 1. In this case the binding profile of 18 human DR allotypes are displayed as columns. The ligands detected are 13-mers and residue number 1 of each 13-mer is identified by a coloured block. The intensity of the binding interaction (High, Medium or Low) for each peptide with respect to each of the 18 allotypes is indicated according to the key displayed. --

Please replace the paragraph beginning at line 14 on page 25 of the specification with the following amended paragraph:

-- **FIGURE 7** is a depiction of the MHC class II ligands identified within epitope region R2 (SEQ ID NO: 3, shown vertically in the first column). Ligands are identified using the *in silico* system of EXAMPLE 1. In this case the binding profile of 18 human DR allotypes are displayed as columns. The ligands detected are 13-mers and residue number 1 of each 13-mer is identified by a coloured block. The intensity of the binding interaction (High, Medium or Low) for each peptide with respect to each of the 18 allotypes is indicated according to the key displayed. --

Please replace the paragraph beginning at line 22 on page 25 of the specification with the following amended paragraph:

-- **FIGURE 8** is a depiction of the MHC class II ligands identified within epitope region R3 (SEQ ID NO: 4, shown vertically in the first column). Ligands are identified using the *in silico* system of EXAMPLE 1. In this case the binding profile of 18 human DR allotypes are displayed

as columns. The ligands detected are 13-mers and residue number 1 of each 13-mer is identified by a coloured block. The intensity of the binding interaction (High, Medium or Low) for each peptide with respect to each of the 18 allotypes is indicated according to the key displayed. --

Please replace the paragraph beginning at line 30 on page 25 of the specification with the following amended paragraph:

-- **FIGURE 9** is a depiction of the MHC class II ligands identified within epitope region R4 (SEQ ID NO: 5, shown vertically in the first column). Ligands are identified using the *in silico* system of EXAMPLE 1. In this case the binding profile of 18 human DR allotypes are displayed as columns. The ligands detected are 13-mers and residue number 1 of each 13-mer is identified by a coloured block. The intensity of the binding interaction (High, Medium or Low) for each peptide with respect to each of the 18 allotypes is indicated according to the key displayed. --

Please replace the paragraph beginning at line 4 on page 26 of the specification with the following amended paragraph:

-- **FIGURE 10** is a depiction of the MHC class II ligands identified within epitope region R5 (SEQ ID NO: 6, shown vertically in the first column). Ligands are identified using the *in silico* system of EXAMPLE 1. In this case the binding profile of 18 human DR allotypes are displayed as columns. The ligands detected are 13-mers and residue number 1 of each 13-mer is identified by a coloured block. The intensity of the binding interaction (High, Medium or Low) for each peptide with respect to each of the 18 allotypes is indicated according to the key displayed. --

Please replace the table beginning after line 10 on page 26 of the specification with the following amended table:

Peptide	Sequence
C-32	Biotin-PKYVKQNTLKLAT (SEQ ID NO: 8) Flu haemagglutinin 307-319
C-49	KVVDQIKKISKPVQH (SEQ ID NO: 9) Chlamydia HSP 60 peptide
KLH	Whole protein from Keyhole Limpet Hemocyanin.